Chapter

Lipid Peroxidation: A Signaling Mechanism in Diagnosis of Diseases

Kalpana Sabanna Patil and Raju Ratan Wadekar

Abstract

Quantification of reactive oxygen species, is perplexing either *in vivo* or *in vitro* due to their short half-lives. Consequently, to define the magnitude of oxidative stress, the more stable oxidation products can be measured in biological samples. The oxidative stress leads to the lipid peroxidation that involves the initiation, termination and propagation of lipid radicals, wherein, the process involves the oxygen uptake, rearrangement of the double bonds in unsaturated lipids, that leads to polyunsaturated fatty acid deterioration. Subsequently, the toxic signaling end products are considered as biomarkers of free radicals that act both as signaling molecules and as cytotoxic products cause covalent alteration of lipid peroxidation products. The use of validated signaling mechanism (s) of Lipid peroxidation and products derived thereof exhibits its use clinical practice and basic clinical research as well as in clinical practice has become common place, and their presence as endpoints in clinical trials is now broadly accepted. This knowledge can be used to diagnose disease earlier, or to prevent it before it starts. The signaling markers can be used to excel the effectiveness of the prevailing medicines and to improve the new medicines.

Keywords: lipid peroxidation, isoprostanes, malondialdehyde, Alzheimer's disease, oxidative stress

1. Introduction

Lipids are of two types: Polar and Non-polar. The polar lipids (Triglycerides), store in various cells but especially in adipose (fat) tissue, are usually the main source of energy for mammals. Polar lipids are underlying segments of cell layers, where in it contributesfor thedevelopment of permeability barrier of cells and sub-cellular organelles in the form of a lipid bilayer [1]. The glycerol-based phospholipid is the significant type of membranous lipid bilayer and it is evidenced by the element that membrane lipids may regulates the biologicalfunctions of a membrane organelle by amending its biophysical characteristics, such as the divergence and absorptivity [2]. Lipids and its metabolite productsfacilitates a key ingredient in understanding the biology and serve as a signaling biomolecules in the diagnosis of diseases [3]. However, theleading enzymes that generate as lipid-signaling biomarkers are lipoxygenase, that intervene hydroperoxyeicosatetraenoic acids (HPETEs), lipoxins, leukotrienes, or hepoxilins biosynthesis after oxidation of fatty acids/arachidonic

acid (AA), cyclooxygenase that yields prostaglandins, and cytochrome P-450 (CYP) that produces epoxyeicosatrienoic acids, leukotoxins, thromboxane, or prostacyclin respectively [4, 5]. The signaling lipid biomarkers recruitsvia stimulation of a variety of receptors, including nuclear and G protein-coupled receptors. Moreover, several othertypes of lipidmetabolites have been recognized as potent intracellular signal transduction molecules viz; i) diacylglycerol (DAG) and inositol phosphates (IPs) were derived from the phosphatidylinositol phosphates. DAG is a transcription nuclear factor-kB (NF-kB) which promotes cell survival and proliferation and also a physiological activator of protein kinase C [6, 7] and a small G protein [8]. On the other hand, IPs (lipid derived metabolites) are anextremelystimulatingthat intricate in signal transduction, results in activation of mTORand Akt [9], and calcium homeostasis [10, 11]; ii) Sphingolipid derived from ceramide (sphingosine-1-phosphate), is aeffective messenger molecule engaged in proliferation, adhesion, migration and alsoregulates calcium mobilization at molecular and cellular level of the organism [12–14]; iii) oxidative stress induced fatty acid derived eicosanoid and prostaglandins involved in inflammation [15, 16] and immunity [17]; iv) phosphotidylserine, (a phospholipid) that plays crucial role in a number of signaling pathways, includes fusogenic proteins, kinases and small GTPases [18]; v) the sex and growth hormones such as testosterone, progesterone, estrogen and cortisol that monitored a host body activities such as reproduction, blood pressure metabolism, inflammation, oxidative stress response etc. [19].

Molecular mechanism of lipid damage: The process of lipid peroxidation (LPO), is the resultant of oxidative stress and free radical production. Specifically, reactive oxygen species (ROS) attack polyunsaturated fatty acids (PUFAs) of cellular membranes and leads tothe insult of functional and/or structural integrity of cell membranes, subsequentlyproducing4-hydroxy-2-noneal (HNE), malondialdehyde (MDA) and acrolein (a group of α, β-unsaturated highly reactive aldehyde) [20, 21]. Therefore, these strong reactive aldehydes are significantlydiffusive, able to attack and form covalent linkages with auxiliary cellular constituents. Moreover, the lipid peroxidation process continues asself-propagation followed by initiation of chain reactions and termination either with complete substrate utilization or through interaction with antioxidants such as tocopherol (Vitamin E). Neuroprostanes (neuroPs), isoprostanes (IsoPs) are the additional LPO products of arachidonic acid and docosahexaenoic acid (DHA), that are quantified in the biological fluids to diagnose the severity of the disease. Furthermore, the cyclized fatty acids proliferate further and metabolize the cellular membrane components, mainly lipids and proteins, and propagates the other LPO products in the body fluids [22].

Quantification of reactive oxygen species, is perplexing either *in vivo* or *in vitro* due to their short half-lives. Consequently, to define the magnitude of oxidative stress, the more stable oxidation products can be measured in biological samples. The oxidative stress leads to the lipid peroxidation that involves the initiation, termination and propagation of lipid radicals, wherein, the process involves the oxygen uptake, rearrangement of the double bonds in unsaturated lipids, that leads to polyunsaturated fatty acid deterioration. Subsequently, the toxic signaling end products are considered as biomarkers of free radicals that act both as signaling molecules and as cytotoxic products cause covalent alteration of lipid peroxidation products [23]. In respect of their oxidative-induced damage properties, these compounds are considered as disease mediators in the pathophysiology of many neurodegenerative diseases (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), Diabetes, Atherosclerosis, Chronic inflammation, Asthma and liver injury that serve as potential biomarkers in the signaling mechanism in diagnosis of diseases [24]. Thus, it is necessary to understand the oxidative deterioration of lipids in a sequential five-step procedure

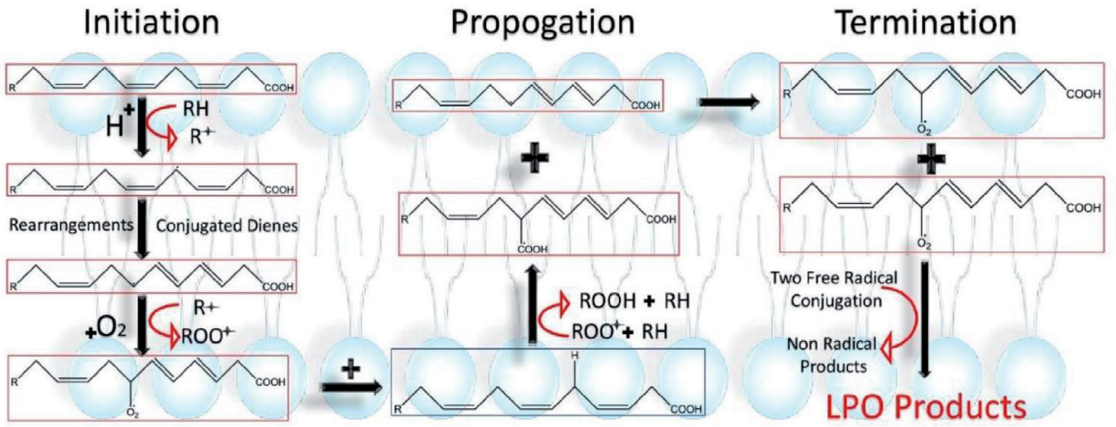

Figure 1.
Oxidative deterioration of lipids.

in which oxidants, either radical or non-radical species, attack lipids containing C-C double bonds [25, 26]. On the contrary of enzyme-based lipid metabolism, lipid peroxidation does follow a non-enzymatic process that continues in ahysterical mode: Initiation, propagation and termination (**Figure 1**) [27].

2. Mechanism of action of lipid peroxidation (LPO)

The process of LPO on membrane influences discrete functions from the increased rigidity of membrane, reduced action of membrane-confined enzymes, impairment of membrane receptors and modified permeability of the cell membrane. Similar to phospholipid impairment, radicals can also directly attack lipid-protein and membrane proteins mediate as well as protein–protein interconnection, subsequently affect the membrane integrity [28]. LPO products persuade such a loss of membrane integrity that ultimately leads to unadorned cytotoxicity, and could result in unrestrained cellular growth or even apoptosis. Rationally, the perturbation of the above-mentioned functions ensued by polyunsaturated fatty acids, along with the resultant metabolites and protein insults modifies the neuronal homeostasis, and leads to the multi-organ organ dysfunction [29–31].

3. Lipid peroxidation (LPO) products as biomarkers in neurodegenerative disorders

LPO products are significantly associated to the development of Alzheimer's diseases (AD); and hence, they are studied as potential disease signaling biomarkers in neurodegenerative disorders. LPO products such as MDA, IsoPs, TBARS, and fluorescent lipofuscin-like pigments (LPF) extensively studied and found in different human samples (plasma, serum and urine) of the patients suffering from neurodegenerative disorders. (Summarized in **Table 1**).

Histopathological studies revealed a co-localization of lipid peroxidation products and β-amyloidplaques in the brain of the AD. Also, the studiy evident for the presence of fatty acids in AD brain lesions produced a neurotoxic effect in cell culture increasing oxidative stress [41]. Since the brain contains high lipid content and high oxygen consumption, lipid peroxidation seems to play fundamental role in AD early detection. Similarly, IsoPsand its isomers produced via diverse actions that, are encountered as marginal oxidation products of the arachidonic acid [42]. Whereas, neuroPsenriched in the neuronal tissue and vital component

Sr. no	Biomarkers	Biological sample	Analytical technique	Results	Reference
01	8-Isoprostane	Urine	EIA	AD <DrD* AD+DM < DrD	[32]
02	Isoprostanes oxidized LDL	Urine	ELISA	Not differences between groups	[33]
03	8-Isoprotanes	Serum	ELISA	Non-frail AD < Pre-frail AD*	[34]
04	Isoprostanes	Urine	EIA	Non-frail AD < frail AD*	[35]
05	Isoprostanes, Neuroprostanes, dihomo-isoprostanes	Urine	RIA	AD + placebo > AD treatment	[36]
06	MDA	Urine	GC–MS	Not differences between groups after the treatment	[37]
07	MDA	Urine	UPLC-MS/MS	Significant differences in groups	[38]
08	MDA	Plasma	HPLC-fluoresce	aMCI converted >aMCI stable	[39]
09	MDA	Blood	HPLC-MS	MDA blood levels do not correlated with different cognitive tests	[40]

Table 1.
Signaling mechanism of lipid peroxidation in biological samples of patients.

of the nervous tissues, awfully susceptible to oxidation [43]. Thus, the quantitative estimation of neuroPsaffords a significantsource of oxidative neuronal impairment-corresponding to IsoPs [44].

Malondialdehyde (MDA) a signaling molecule of LPO has ability to interact with micro-macromolecules such as nucleic acid bases, developingdivergent adducts, and can also react with proteins in a synergistic and covalent manner, subsequently, leads to the stimulation of strong immune responses and exhibits pro-fibrogenic and pro-inflammatory properties/mediators such as interleukins, cytokines etc. Furthermore, accumulation of MDA modifies membrane integrity by inducing increased intra and extracellular permeability and damage the fluidity of membrane lipid bilayer. Being a most mutagenic, MDA is capable of reacting with deoxyadenosine in DNA and deoxyguanosine, thus generating mutagenic DNA adducts [21, 31].

As the consequence of peroxidation of PUFAs (linoleic and arachidonic acid), Hudroxy-2-nonrenal (HNE) are formed, since they are the most abundant in fatty acids. The HNE, specifically, bind to amino acids mainly: cysteine, histidine and lysine proteinaceous residue addition by either the amino and thiol groups. The conjugates of protein residue and HNE, leads to the impairment of the normal protein function as well as structure, and also HNE exhibits reactivity with vital nucleic acids, lipids, signaling biomolecules and vitamins. Documented reports, suggests that, the HNE accumulates in extremely low concentration (10 μM), in response to oxidative stress and induces cytotoxicity and selective suppression of inducible and basal NF-kB factors. Therefore, increased levels of HNE results in Ca^{2+} homeostasisimbalance, disruption of glutamate transport, membrane impairment, microtubule function, and cellular death via the activation of caspase pathways [28, 45].

Threonine metabolite product, acrolein generated by the bio activation of phagocytes and cyclophosphamide. Wherein, acrolein targets histidyl, lysyl and cysteinyl residue of protein side chain as well as reactswith nucleophilic sites in DNA, that results in DNA and protein adducts and, thus, initiates cytotoxicity specifically related to its ability to reduce glutathione [46]. Docosahexaenoic acid (DHA) enriched in neurons, and is a vital compound of the nervous tissue. It is a vital compound of the nervous tissue and enriched in neurons and extremely-susceptible to oxidation. DHA on oxidative stress, leads to the production of Neuroprostanes (F4-isoprostanes). In a biological aspect, neuroPsillustrates anti-inflammatory properties by inhibiting proteasome concentrated in the neurons membrane [45]. Nevertheless, the central nervous system (CNS) is one of the major targets of the LPO and proneto chain reactions induced by ROS, which eventually result in LPO products [47]. The role of LPO quantification in the pathogenesis of NDs is significant and extremely importance for the early detection of neurodegenerative disorders [45].

The most frequently exploited LPO products such as lysine residues and unsaturated aldehydes, including HNE and aracolein [48]. Several research studies have been probing the LPO products and disease state interrelation, and its application as possible biomarkers in order to assess prognosis and establish early detection of the disease [49]. Among the above-mentioned potential biomarkers, IsoPssignifies the most reliable and robust outcomes. Moreover, the IsoPs accurately process and assessed the oxidant stress *in vivo*via quantification of plasma and urinary sample. Also, *in situ* phospholipids composed of IsoPs that locates the free radical production and release from the cellular membrane via phospholipases in the plasma. IsoPs detected and quantified in a plethora of biological fluids including plasma cerebrospinal fluid, exhaled breath condensate, urine and bile [50]. On the other hand, neuroPs are a fundamental component of the nervous tissue, enriched in the neuronal tissue and extremely susceptible to oxidation [51]. Thus, the quantification of neuroPs provides a signaling biomarker of oxidative neuronal damage compare to IsoPs quantification. In addition, the quantity of neuroPs produced

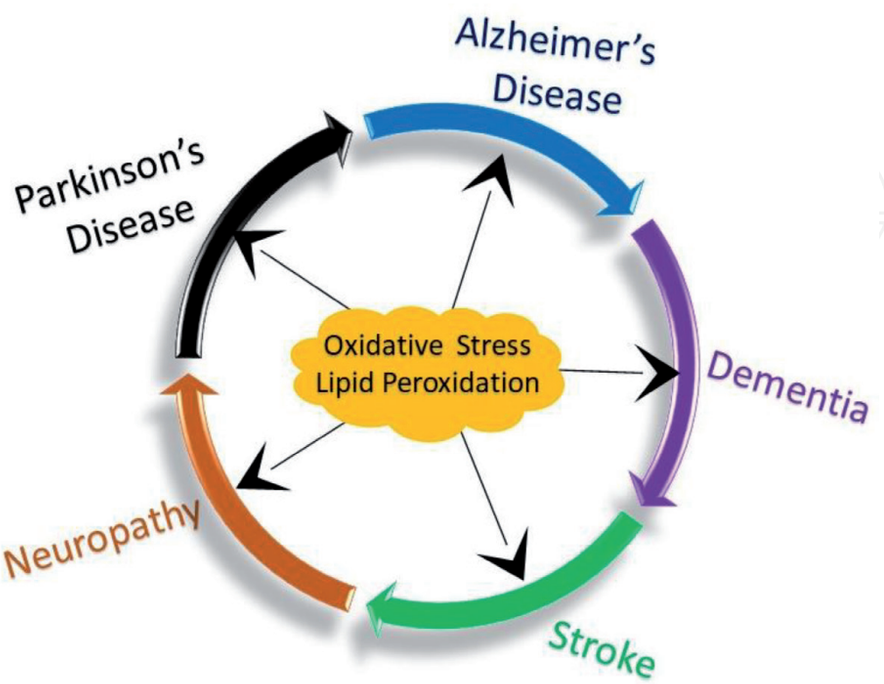

Figure 2.
Lipid peroxidation (LPO) products as biomarkers in neurodegenerative disorders.

from DHA surpass that of IsoPs from arachidonic acid by 3.4 folds. NeuroPsare elevated in the cerebrospinal fluid and brain tissue in ND, such as Parkinson and Alzheimer's disease. Hence, quantification of neuroPs levels isa vital tool in evaluating brain oxidative impairment [52]. Whereas, crosslinking is a major factor in the development of pathology due to the promotion of intramolecular or intermolecular DNA and protein cross-linking, which results in intense change in the biochemical properties of various biomolecules (**Figure 1**). This articulated process is assumed to be a channel of interrelation chain reactions with covalent nucleophilic compounds. Also, the translated and interconnected experimental indicators with precise altered proteins in the CNS exhibited those definite cellular amendments are in concomitant with pathophysiology of Neurodegenerative diseases. Thus, the revival of scientific data affords a comprehensive knowledge in the advancement and employment of LPO products as potential biomarkers in the early diagnosis of the disease, alteredbiological processes, revealing potential active sites to target disease progression (**Figure 2**).

4. Lipid peroxidation metabolites as influential signaling biomarkers in asthma and airway inflammation

Oxidative stress at molecular and cellular level can have many detrimental effects on airway function, including airway smooth muscle contraction, induction of airway hyper responsiveness, mucus hypersecretion, vascular exudation and shedding of epithelial cells. Furthermore, ROS can induce cytokine and chemokine production through induction of the oxidative stress-sensitive transcription of nuclear factor–kB in bronchial epithelial cells [53]. Recently discovered series of bioactive prostaglandin (PF)F2-like compoundswere produced independently of the cyclooxygenase enzymes via the peroxidation of arachidonic acid, catalyzed by free radicals. The pathway leads to formation of 64 isomeric structures, of which 8-iso-PGF2α is most well characterized. Evidence suggests that 8-iso-PGF 2α may act in part through the vascular thromboxane A2/PGH2 (TP) receptor [54]. 8-iso-PGF2α has been found to elicit airway hyper-responsiveness in isolated perfused mouse lungs, and cause airway obstruction and air plasma exudation in guinea pigs in *vivo* [55]. These experimental findings offerassumption about the contribution of Isoprostanes to the airway narrowing that is characteristic of asthma and in addition to being reliable signaling marker of lipid peroxidation, Isoprostane may prove to have an important biological role in the pathological of asthma. A significant elevation of reactive oxygen species, MDA formation (A product of Lipid peroxidation) and Isoprotane was estimated in the broncho-alveolar lavage (BAL) fluidwithin 24 hrs of allergen-induced asthma. This clearly indicates, Isoprotane is produce as a biomarker in respiratory tract tissues that leads to the late observed physical symptoms in allergen-induced asthma [56].

A recent study demonstrated that concentrations of exhaled ethane were increased in patients with more severe bronchoconstriction (forced expiratory volume in one second (FEV1) <60%), compared with less-constricted patients (FEV1 > 60%) and provides evidence that lipid peroxidation is related to asthma severity. These relationships between markers of oxidative stress and disease severity suggest that such tests may indicate the clinical status of asthma patients [57]. The increased level of 8-sio-PGF2α concentrations has been observed in chronic obstructive pulmonary diseases and asthma [58]. The discovery of Isoprostane has generated attention, as they provide a reliable index of oxidative stress *in vivo*. Isoprostane are structurally stable, are produced *in vivo* and are present in relatively high concentrations [59]. Traceable levels of F2-isoprostanes can be found in all normal animal and

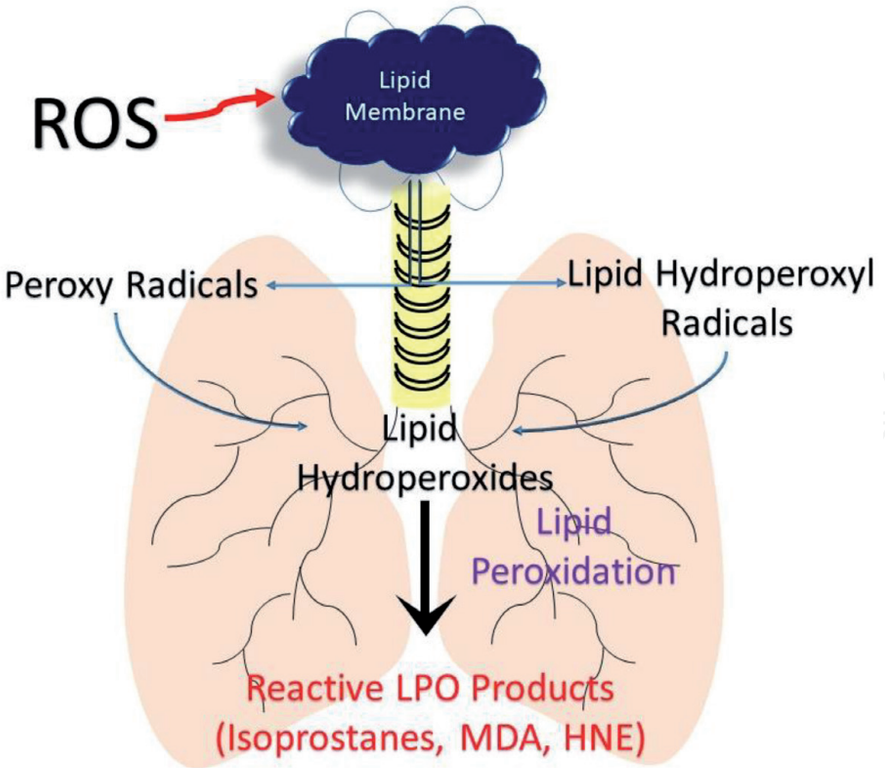

Figure 3.
Lipid peroxidation metabolites as influential signaling biomarkers in lung diseases.

human biological fluids (including plasma, urine, bile, gastric juice, synovial fluid and cerebrospinal fluid)), and esterified in normal animal tissues. Thus, they overcome many of the methodological problems associated with other signaling markers. Determination of 8-iso-PGF2αas a marker of oxidative stress, of carbon tetrachloride (CCl_4)-induced lipid peroxidation has been shown to be 20 times more sensitive than measurement of Thiobarbituric acid reactive substances (TBARS). Thus, the reliability of isoprostanes as in vivo markers of lipid peroxidation makes them an extremely valuable signaling biomarker for defining the potential of antioxidant agents (Vitamin C, E and β-carotene) in humans [60]. A significant amount of elevated ethane produced following lipid peroxidation has been observed in plasma and breath condensate of asthmatics as a biomarker indicator of acute airway inflammatory diseases. Moreover, measurement of auto-antibodies directed against oxidative modifications of low density lipids (LDL) is a recently developed technique that provides an in vivo marker of lipid peroxidation. Enzymes-linked immunosorbent assays are available in kit form, providing a quick and simple methodology. Thus measurement of isoprostanes in breath condensate should provide useful information concerning the degree of oxidant stress and success of antioxidant therapy in asthma (**Figure 3**).

5. Lipid peroxidation: a signaling mechanism in diagnosis of liver injury

Oxidative stress is one of the mechanisms involved in the pathogenesis of drug-induced reactive oxygen species which lead to the depletion of intracellular antioxidants, causing an imbalance in the redox status of the hepatic cells [61]. Rapid, extensive lipid peroxidation of the membrane structural lipids due to oxidative stress mechanism involved in the pathogenesis of drug-induced had seen proposed as the basis of drug-induced hepatocellular toxicity. The most of the xenobiotics such as Acetaminophen, Isoniazid and Rifampicin are well-known to

induced hepatic damage directly or indirectly via lipid peroxidation [62]. However, peroxy radical attribute to lipid peroxidation, thus known for the destabilization and disintegration of the cell membrane, that further causes arteriosclerosis, hepatic and kidney damage. The increased serum markers such as MDA formation are of diagnostic importance of hepatic injury because they are released due to the damage of hepatocytes and consequently participate in endogenous enzymatic antioxidant system imbalance [63]. CCl4-ehanced lipid peroxidation has been observed in liver tissue homogenates, isolated hepatocytes and in vivo, and this has been associated with changes in endoplasmic reticular enzyme activity, in vivo fatty acid export and protein synthesis [64]. CCL4 metabolism enhances production of malondialdehyde in vitro and increase ethane production and lethality in vivo (**Figure 4**). Consequently, lipid peroxidation initiated by free radical reactions and unchecked by compromised cellular defenses, provides a possible link between

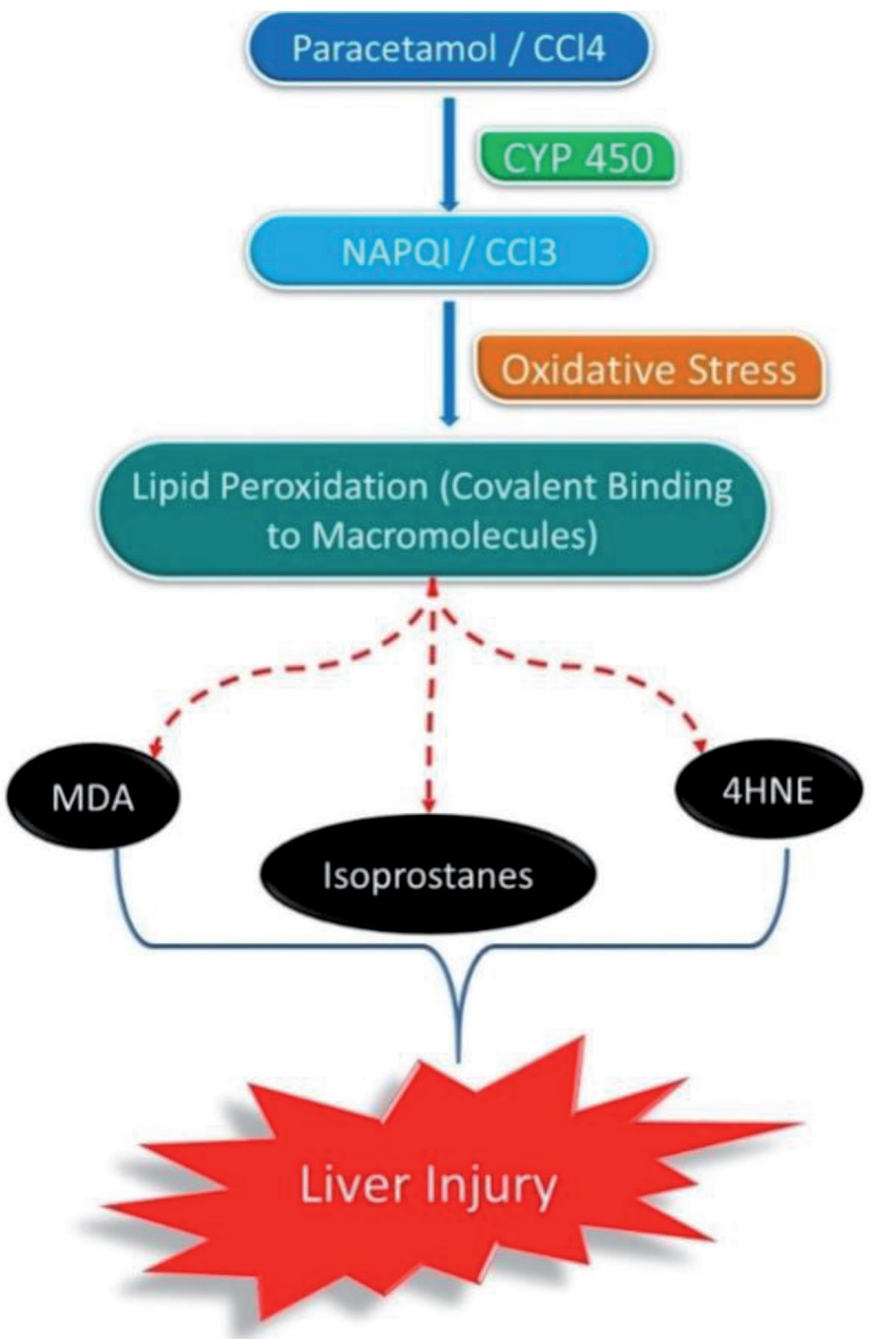

Figure 4.
Lipid peroxidation: a signaling mechanism in diagnosis of liver injury.

ethanol metabolism and associated liver disease [65]. The lipid peroxide content of liver is elevated by both short and long-term ethanol exposure and an enhanced rate of lipid peroxide formation following ingestion has been ascertained by MDA production, diene conjugate formation and *in vivo* ethane and pentane exhalation. Lipid peroxidation might merely be a sign of oxidative processes which occur after reduced glutathione is depleted concomitant with free radical attack on cellular protein and nucleic acid. The elevated MDA formation as a product of lipid peroxidation in drug-induced liver damage provide a significant biological signaling marker for the early detection or diagnosis of liver injury.

6. Conclusion

The oxidative stress inducing compounds mediates metabolic process of lipids mainly via peroxidation that leads to the production of macromolecules such as Isoprostane, MDA, 4-HNE in the biological fluids. Moreover, the aldehyde like molecules produced via lipid peroxidation targets and modifies proteins and DNA substantially at macromolecule level. Furthermore, MDA and 4-HNE known to promote cross linking of protein/DNA reactions that significantly alleviates and alters the biomarkers biochemical property, thereby develops a clinical symptomatic states. The use of validated signaling mechanism (s) of Lipid peroxidation and products derived thereof in basic and clinical research as well as in clinical practice has become common place, and their presence as endpoints in clinical trials is now broadly accepted. This knowledge can be used to diagnose disease earlier, or to prevent it before it starts. The signaling markers can be used to improve the efficacy and safety of existing medicines and to develop new medicines.

Conflict of interest

The authors declare no conflict of interest.

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